

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A compound that binds to an mpl receptor comprising the structure

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wherein TMP_1 and TMP_2 are each independently selected from the group of core compounds comprising the structure:

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wherein,

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X_2 is selected from the group consisting of Glu, Asp, Lys, and Val;

X_3 is selected from the group consisting of Gly and Ala;

X_4 is Pro;

X_5 is selected from the group consisting of Thr and Ser;

X_6 is selected from the group consisting of Leu, Ile, Val, Ala, and Phe;

X_7 is selected from the group consisting of Arg and Lys;

X_8 is selected from the group consisting of Gln, Asn, and Glu;

X_9 is selected from the group consisting of Trp, Tyr, and Phe;

X_{10} is selected from the group consisting of Leu, Ile, Val, Ala, Phe, Met, and Lys;

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L_1 is a linker; and

n is 0 or 1;

and physiologically acceptable salts thereof.

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2. The compound according to Claim 1 wherein said TMP_1 and TMP_2 are independently selected from the group consisting of:

$X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}$;
 $X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}$;
 $X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}$;
 $X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14}$;
5 $X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}$;
 $X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}$;
 $X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}$;
 $X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}$; and
 $X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14}$,

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wherein $X_2 - X_{10}$ are as defined;

X_1 is selected from the group consisting of Ile, Ala, Val, Leu, Ser, and Arg;

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X_{11} is selected from the group consisting of Ala, Ile, Val, Leu, Phe, Ser, Thr, Lys, His, and Glu;

X_{12} is selected from the group consisting of Ala, Ile, Val, Leu, Phe, Gly, Ser, and Gln;

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X_{13} is selected from the group consisting of Arg, Lys, Thr, Val, Asn, Gln, and Gly; and

X_{14} is selected from the group consisting of Ala, Ile, Val, Leu, Phe, Thr, Arg, Glu, and Gly.

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3. The compound according to Claim 1 wherein said TMP_1 and/or TMP_2 are derivatized as set forth in one or more of the following:

one or more of the peptidyl [-C(O)NR-] linkages (bonds) have been replaced by a non-peptidyl linkage such as a - CH_2 -carbamate linkage [- CH_2 -OC(O)NR-]; a phosphonate linkage; a - CH_2 -sulfonamide [- CH_2 -S(O)₂NR-] linkage; a urea [-NHC(O)NH-] linkage; a - CH_2 -secondary amine linkage; or an alkylated peptidyl linkage [-C(O)NR⁶- where R⁶ is lower alkyl];

the N-terminus is a -NRR¹ group; to a -NRC(O)R group; to a -NRC(O)OR group; to a -NRS(O)₂R group; to a -NHC(O)NHR group where R and R¹ are hydrogen and lower alkyl with the proviso that R and R¹ are not both hydrogen; to a succinimide group; to a benzyloxycarbonyl-NH- (CBZ-NH-) group; or to a 5 benzyloxycarbonyl-NH- group having from 1 to 3 substituents on the phenyl ring selected from the group consisting of lower alkyl, lower alkoxy, chloro, and bromo;

the C terminus is -C(O)R² where R² is selected from the group consisting of lower alkoxy and -NR³R⁴ where R³ and R⁴ are independently selected from the 10 group consisting of hydrogen and lower alkyl.

4. The compound according to Claim 1 wherein all of the amino acids have a D configuration.

15 5. The compound according to Claim 1 wherein at least one of the amino acids has a D configuration.

6. The compound according to Claim 1 which is cyclic.

20 7. The compound according to Claim 1 wherein TMP₁ and TMP₂ are each

Ile-Glu-Gly-Pro-Thr-Leu-Arg-Gln-Trp-Leu-Ala-Ala-Arg-Ala. (SEQ ID NO: 1)

8. The compound according to Claim 1 wherein L₁ comprises a peptide.

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9. The compound according to Claim 8 wherein L₁ comprises Y_n, wherein Y is a naturally-occurring amino acid or a stereoisomer thereof and n is 1 through 20.

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10. The compound according to Claim 8 wherein L₁ comprises (Gly)_n, wherein n is 1 through 20, and when n is greater than 1, up to half of the Gly residues may be substituted by another amino acid selected from the remaining 19 natural amino acids or a stereoisomer thereof.

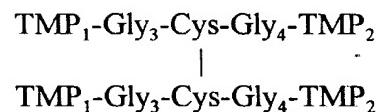
11. The compound according to Claim 8 wherein L₁ is selected from the group consisting of

- (Gly)₃Lys(Gly)₄ (SEQ ID NO: 6);
5 (Gly)₃AsnGlySer(Gly)₂ (SEQ ID NO: 7);
(Gly)₃Cys(Gly)₄ (SEQ ID NO: 8); and
GlyProAsnGly (SEQ ID NO: 9).

12. The compound according to Claim 8 wherein L₁ comprises a Cys residue.

13. A dimer of the compound according to Claim 12.

14. The dimer according to claim 13 which is



20 15. The compound according to Claim 1 wherein L₁ comprises (CH₂)_n, wherein n is 1 through 20.

25 Sub R₃
16. The compound according to Claim 1, which is selected from the group consisting of

IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA (SEQ. ID NO: 9)

30 IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (cyclic) (SEQ. ID NO: 10)

IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (linear) (SEQ. ID NO: 11)

IEGPTLRQALAARA-GGGGGGGG-IEGPTLRQALAARA (SEQ. ID NO: 12)

IPEGPTLRQWLAARA-GGGKGGGG-IPEGPTLRQWLAARA (SEQ. ID NO: 13)

IPEGPTLRQWLAARA-GGGK(BrAc)GGGG-IPEGPTLRQWLAARA
5 (SEQ. ID NO: 14)

IPEGPTLRQWLAARA-GGGCGGGG-IPEGPTLRQWLAARA (SEQ. ID NO: 15)

IPEGPTLRQWLAARA-GGGK(PEG)GGGG-IPEGPTLRQWLAARA
10 (SEQ. ID NO: 16)

IPEGPTLRQWLAARA-GGGC(PEG)GGGG-IPEGPTLRQWLAARA
15 (SEQ. ID NO: 17)

IPEGPTLRQWLAARA-GGGNGSGG-IPEGPTLRQWLAARA (SEQ. ID NO: 18)

IPEGPTLRQWLAARA-GGGCGGGG-IPEGPTLRQWLAARA
20 IPEGPTLRQWLAARA-GGGCGGGG-IPEGPTLRQWLAARA (SEQ. ID NO: 19);

IPEGPTLRQWLAARA-GGGGGGGG-IPEGPTLRQWLAARA (SEQ. ID NO: 20).

17. The compound according to Claim 1 or 2, which has the formula

25 $(Fc)_m-(L_2)_q-\underbrace{TMP_1-(L_1)_n-TMP_2-(L_3)_r}_{-}(Fc)_p$

wherein L_1 , L_2 and L_3 are linker groups which are each independently selected from the linker groups consisting of

30 Y_n , wherein Y is a naturally-occurring amino acid or a stereoisomer thereof and n is 1 through 20;

35 $(Gly)_n$, wherein n is 1 through 20, and when n is greater than 1, up to half of the Gly residues may be substituted by another amino acid selected from the remaining 19 natural amino acids or a stereoisomer thereof;

(Gly)₃Lys(Gly)₄ (SEQ ID NO: 6);

(Gly)₃AsnGlySer(Gly)₂ (SEQ ID NO: 7);

5 (Gly)₃Cys(Gly)₄ (SEQ ID NO: 8);

GlyProAsnGly (SEQ ID NO: 9);

a Cys residue; and

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(CH₂)_n, wherein n is 1 through 20

Fc is an Fc region of an immunoglobulin; m, p, q and r are each independently selected from the group consisting of 0 and 1, wherein at least one of m or p is 1, and further wherein if m is 0 then q is 0, and if p is 0, then r is 0; and physiologically acceptable salts thereof.

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18. The compound according to Claim 17 wherein L₁, L₂ and L₃ are each independently selected from the group consisting of Y_n, wherein Y is selected a naturally-occurring amino acid or a stereoisomer thereof and n is 1 through 20.

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19. The compound according to Claim 18 wherein L₁ comprises (Gly)_n, wherein n is 1 through 20, and when n is greater than 1, up to half of the Gly residues may be substituted by another amino acid selected from the remaining 19 natural amino acids or a stereoisomer thereof.

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20. The compound according to Claim 18 wherein L₁, L₂ and L₃ are independently selected from the group consisting of

30 (Gly)₃Lys(Gly)₄ (SEQ ID NO: 6);

(Gly)₃AsnGlySer(Gly)₂ (SEQ ID NO: 7);

(Gly)₃Cys(Gly)₄ (SEQ ID NO: 8); and

GlyProAsnGly (SEQ ID NO: 9).

21. The compound according to Claim 18 wherein L₁, L₂, or L₃ comprises a Cys residue.

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22. A dimer of the compound according to Claim 21.

23. The compound according to Claim 17 wherein L₁, L₂ or L₃ comprises (CH₂)_n, wherein n is 1 through 20.

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24. The compound according to Claim 1, which is selected from the group consisting of

15 Fc-IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA (SEQ. ID NO: 21)

18 Fc-IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA-Fc (SEQ. ID NO: 22)

20 IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA-Fc (SEQ. ID NO: 23)

25 Fc-GG-IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA (SEQ. ID NO: 24)

30 Fc-IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 25)

25 Fc-IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (cyclic) (SEQ. ID NO: 26)

30 Fc-IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (linear) (SEQ. ID NO: 27)

Fc-IEGPTLRQALAARA-GGGGGGGG-IEGPTLRQALAARA (SEQ. ID NO: 28)

35 Fc-IEGPTLRQWLAARA-GGGKGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 29)

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Fc-IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 30)

Fc-IEGPTLRQWLAARA-GGGNGSGG-IEGPTLRQWLAARA (SEQ. ID NO: 31)

5 Fc-IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA

Fc-IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 32)

10 Fc-GGGGG-IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA
(SEQ. ID NO: 33).

25. A method of increasing megakaryocytes or platelets in a patient in need thereof, which comprises administering to said patient an effective amount of a compound according to Claim 1.

15 26. The method according to Claim 25, wherein said amount is from 1 µg/kg to 100 mg/kg.

20 27. A pharmaceutical composition comprising a compound according to Claim 1 in admixture with a pharmaceutically acceptable carrier thereof.

28. A polynucleotide that encodes a compound according to claim 8.

29. A polynucleotide that encodes a compound according to claim 13.

25 30. A polynucleotide that encodes a compound according to claim 18.

31. A polynucleotide that encodes a compound according to claim 22.

30 32. A vector that comprises a polynucleotide according to any of claims 28-31.

33. A host cell that comprises a vector according to claim 32.

34. A method of producing a compound according to claims 8, 13, 18 or 22, which comprises growing a host cell according to claim 33 in a suitable nutrient medium and isolating said compound from said cell or nutrient medium.

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